phase". Following Applicant's response to the Office Action of July 18, 1988, in Applicant's immediate prior application 07/061,646, the rejection over Pasquale was withdrawn.

Pasquale, U.S. Patent 4,544,554, does not teach an increasing level of estrogen in its triphasic composition. Pasquale clearly teaches that the estrogen level be maintained constant in each phase of its triphasic composition. For example, in the Abstract on the face of the Pasquale patent, the triphasic composition is clearly stated as containing an estrogen component of 0.02-0.05 mg in phase one and the same dosage in phase two and the same dosage in phase three. In column 1 of the '554 patent the object of the Pasquale composition is noted on lines 47-50: "These findings have prompted a greater emphasis on a reduction of the progestogen dosage in oral contraceptives." Further, on lines 54 to 58, it is stated: "By the present invention a triphasic oral contraceptive regimen is provided wherein the estrogen dosage is kept constant throughout the 21-day cycle while the progestogen dosage is gradually increased in successive doses" (our emphasis added). The constant estrogen dosages are repeated again in column 2 at line 11 as a proviso to the description of the compositions.

Thus, in reading the reference as a whole, it is clear that the invention of Pasquale is opposite to that presently claimed. Pasquale claims a constant dose estrogen triphasic with an increasing progestogen dose. Contra thereto, the present invention is directed to a low dose estrogen triphasic composition where the estrogen dose is increased in each phase. There is absolutely no suggestion in Pasquale to combine ethinyl estradiol and norethindrone acetate in a triphasic composition where the level of estrogen is increased in each phase. Absent such a suggestion, the present invention cannot be deemed obvious.

An invention is not obvious merely because it is a combination of old elements each of which were well known in the art at the time the invention was made, Reiner v. I. Leon Co., Inc., 128 USPQ 25. Rather, if such a combination as the present combination is novel, the issue is whether bringing them together as taught was obvious in light of the prior art, United States v. Adams, 148 USPQ at 483. The critical inquiry is whether "there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination", Lindemann Maschinenfabrik GMBH v. American

Hoist and Derrick Co., 221 USPQ at 488. The case which most clearly demonstrates the state of the current law in that there must be a clear suggestion of the claimed subject matter in the prior art is Kimberly-Clark Corp. v. Johnson & Johnson, 223 USPQ 603. Also, a clear discourse on the present law on obviousness is reported in Gillette Co. v. S. C. Johnson & Son Inc., 12 USPQ2d at 1929.

In view of the above, the rejection of the claims under 35 U.S.C. 103 over Pasquale should be withdrawn.

Reconsideration is also respectfully requested of the rejection of claims 1-9 under 35 U.S.C. 103 as allegedly being unpatentable over De Jager, Pitchford and Edgren. To analyze correctly the Patent Office's rejection over these three references, there must be a clear understanding of what the references teach.

The De Jager patent, U.S. 4,378,356, teaches a multiphase combination-type sequential preparation for oral contraception wherein the estrogen employed in each phase decreases starting with a high estrogen dose in the first phase. At the same time the dose of gestagen is increased from a small dose in the first phase or practically no unopposed estrogen content in the first phase to increasing doses in the second and equal or increasing doses in the third phase. In addition, the gestagen employed is related to naturally occurring hormones and does not encompass norethindrone acetate as noted in column 3, lines 19 to 34. In contrast to De Jager, the present invention starts with a low dose of estrogen and increases in dose in each phase where the progestogen or the norethindrone acetate specifically claimed in the present invention is either constant or increased slightly in the second phase. Thus the composition as claimed in the present invention is entirely different and, in fact, opposite to that taught in De Jager. There is absolutely no suggestion in De Jager to use an increasing estrogen dose in its multiphase combination.

The Pitchford reference, U.S. Patent 4,425,339, is respectfully submitted to be irrelevant to the invention claimed. The Pitchford patent is not directed to an oral contraceptive composition. It is directed to a composition and a method for treating menopausal symptoms, see the front page of the '339 patent and the abstract on that page. Also, it is clear from the front page of the patent that a high dose of estrogen is used in the three phases with an increase in estrogen dose perhaps at the third phase. Also, the first phase

contains estrogen only and does not contain the progestin or norethisterone noted in phases B and C. A third difference is the use of a natural estrogen as opposed to ethinyl estradiol as claimed in the present invention. In view of the many differences and the different use, the teaching of Pitchford clearly does not suggest the present invention and cannot be considered in combination with the De Jager and Edgren references cited. The references cannot be combined absent a suggestion to combine and there is no suggestion in Pitchford for using its compositions as oral contraceptives. Furthermore it is clear that the high dose of estrogen totally defeats the purposes of not only the present invention but the teachings in the oral contraceptive compositions of the remaining prior art cited.

The Edgren patent, U.S. 4,390,531, is very similar to the Pasquale patent, cited in the previous rejection. The Edgren patent also teaches a constant dose of estrogen in its multiphase combination, see abstract on the face of the '531 patent. In column 1, lines 35 to 38, Edgren clearly states that the present invention is designed to minimize the side effect of breakthrough bleeding by optimizing the amount of progestogen administered at the midpoint of the cycle. Thus the feature of Edgren is using a constant dose of estrogen and using twice the dose of progestogen in the second phase as was administered in the first phase followed by a lowering of the progestogen back to the same level as phase one in phase three. On this basis it is again clear that there is absolutely no suggestion in Edgren to a multiphase contraceptive combination where the dose of estrogen is increased in each phase as claimed in the present invention.

If one were to combine the teachings of Edgren and De Jager, the suggestion would be either to have a multiphase combination where the estrogen content is constant and the gestagen or progestogen increased at least in the mid-phase or phase two or varying the estrogen by starting with a high dose and ending with a low dose in the third phase. If there is a suggestion to combine such references, the suggestion is teaching away from the invention claimed herein. On this basis, the present claims are not obvious over the three references cited by the Office, see the cases cited in the above argument on the Pasquale rejection.

It is respectfully submitted that the criterion being used in the above rejections is "obvious to try" which is well

established in law to be improper, see the application of Henderson, 146 USPQ 372, and the application of Huellmantel, 139 USPQ 496. In addition, it has also been held that in connection with obvious to try: "mere fact that prior art could be modified ... does not make modification obvious unless prior art suggested desirability of modification". See In re Gordon et al., 221 USPQ 1125. Therefore, the modification of a composition containing ethinyl estradiol and norethindrone acetate known to be used in multiphase combinations is not obvious because none of the references suggest the desirability of such a modification where the low estrogen level is increased in each phase.

In addition to the above, Applicant attaches with the present amendment secondary evidence which was made of record in Applicant's prior continuation-in-part application Serial Number 07/061,646. This is a publication in Contraception, June 1987, Volume 35, No. 6, reporting on a clinical study which compared one of the compositions of the present invention to three different fixed dosages of oral contraceptives where the estrogen dose in one instance is 20 µg, 30 µg in a second instance and 50 µg in the third. As stated in the last three sentences of the abstract of the article, the new formulation, meaning the formulation as claimed in the present invention, produced the lowest rate of breakthrough bleeding (BTB) compared with the other three products. All four combination oral contraceptives resulted in an increase in high-density lipoprotein cholesterol (HDL-C). The levels of HDL-C were greatest with Estrostep™. Estrostep™ refers to the triphasic composition using graduated estrogen dosages as claimed in the present invention. A further analysis of the clinical studies was made of record by a Declaration Under Rule 132 of Dr. Leon Speroff, a recognized physician in the field of Obstetrics and Gynecology and having a subspeciality certification in the division of Reproductive Endocrinology. Dr. Speroff, a consultant for Warner-Lambert, analyzed the results of the clinical studies and particularly pointed out the advantages of the graduated estrogen product over the three products compared. Additionally, he pointed to advantages of the present invention over the 1/30 µg product by analyzing the weekly data which was not reported in the Contraception publication.

Finally, Dr. Speroff noted the advantages of the graduated estrogen product on cholesterol-lipoprotein profile. In support of the data in Contraception and his remarks, there is also

attached and copied herein separate publications on the effects of oral contraceptives on plasma lipids and lipoproteins.

The entire package of evidence submitted is attached for the Examiner's review and further consideration of the rejections.

In conclusion, it is respectfully submitted that there is nothing in the prior art which would have counselled against using a graduated estrogen multiphase combination containing ethinyl estradiol and norethindrone acetate. There is nothing in the prior art to indicate "disadvantages" in the present claimed formulations. In short, there is nothing in the prior art to deter any investigation into such combination. But, there is no clear suggestion of the claimed subject matter in the prior art either. Therefore, proceeding in a way that is contrary to the prior art, namely using a graduated estrogen combination as opposed to a constant or decreasing estrogen combination, and succeeding is a solid indication that the subject matter is not obvious, Gillette Co. v. S. C. Johnson & Son Inc., 12 USPQ2d 1929 at 1957 and the cases cited, namely Kimberly-Clark Corp. v. Johnson & Johnson, 223 USPQ at 603 and Hybritech v. Monoclonal Antibodies, Inc. 231 USPQ at 93.

A prompt and favorable reply is earnestly solicited.

Respectfully submitted,

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RAD:cm/568
Enclosures